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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,706	10/20/2003	Joseph Loscalzo	102258.170 US2	2830

25270 7590 10/26/2007

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
10/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,706	LOSCALZO ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,13 and 16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,13 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/20/2007, NO 1449submitted*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Request for continued examination (i.e., RCE) under 37 CFR §1.114, including the fee set forth in 37 CFR §1.17(e), was filed in this application on 02 August 2007 after an Advisory Action mailed was mailed on 20 July 2007 and a Final action mailed 26 March 2007. Since this application is eligible for continued examination under 37 CFR §1.114, and the fee set forth in 37 CFR §1.17(e) has been timely paid, the finality of the previous Office action mailed 26 March 2007. has been withdrawn pursuant to 37 CFR §1.114. Amendment and Response filed 02 August 2007 is acknowledged and has been entered. Accordingly an RCE has been established and the action on RCE follows.

2. The responses filed 02 August 2007 and 20 June 2007 are acknowledged and entered.

3. In view of remarks and amendment filed 20 June 2007 and remarks filed 02 August, the following rejection in the Office Action mailed 26 March 2007 is hereby withdrawn:

- obviousness rejection to Claims 1-13 and 16-25 under 35 U.S.C. §103 (a) as obvious over combined teachings from Birch et al (U.S. Patent 5,627,191) in view of Cohn (U.S. Patent 4,868, 179) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims Status

4. Claims 10-11 have currently been cancelled.

5. Claims 14-15 and 26-129 remain cancelled.

6. Claims 1-9, 12-13 and 16-25 are pending and are examined on merits.

Objection to Information Disclosure Statement

7. The information disclosure statement filed 20 June 2007 is deficient because there is no USPTO Form 1449 or equivalent filed along with said IDS.

Rejections Under 35 U.S.C. § 102(b)

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

9. Claims 1-4, 6-9 and 16-18 are rejected under 35 U.S.C. §102(b) as anticipated by Cohn (U.S. Patent 4,868, 179).

Claims recite a sustained release composition comprising a small molecule antioxidant and isosorbide dinitrate, wherein the antioxidant is a hydralazine compound, namely hydralazine hydrochloride. In said composition, the isosorbide dinitrate is in range of 30 milligrms/ day to 160 milligrams/day and hydralazine hydrochloride in rang of 30 milligrams to 400 milligrams/day and is in a solid dose as a tablet or capsule. Said composition further comprises a pharmaceutically acceptable carrier

Regarding Claims 1-4, 6-9 and 16-18, Cohn teaches a composition in form of tablet or capsule, wherein said composition comprises a daily dose in range of 55 milligrams/day to 3, 000 mg/day of hydralazine hydrochloride and 30 milligrams/day to 160 milligrams/day of isosorbide dinitrate (Column, Lines 5-8; Column 3, Lines 19-47). Since the unit dose is in form of capsule and/or tablet, it is solid and is comprised of a pharmaceutical carrier and the composition of each of the components is within the range of the dosage instantly claimed.

Therefore, Cohn anticipates the composition clamed in Claims 1-4, 6-9 and 16-18.

Rejections Under 35 U.S.C. § 103(a)

10. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C.§ 103(a).

12. Claims 1-4, 6-9, 12-13 and 16-25 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Cohn (U.S. Patent 4,868, 179) in view of Klemsdal et al. ((1994. A New Isosorbide Dinitrate Extended-Release Formulation: Pharmacokinetic and Clinical Parameters in Patients with Stable Angina Pectoris. Eur. J. Clin. Pharmacol., 47:351-354) with evidence from Wikipedia (Anonymous, Isosorbide mononitrate. From Wikipedia Pages 1-4 Printed 10/18/2007) and further in view of Chobanian et al (U. S. Patent 5,645,839).

Claims recite a sustained release composition comprising a small molecule antioxidant and isosorbide dinitrate, wherein the antioxidant is a hydralazine compound, namely hydralazine hydrochloride. In said composition, the isosorbide dinitrate is in range of 30 milligrms/ day to 160 milligrams/day and hydralazine hydrochloride in rang of 30 milligrams to 400 milligrams/day and is in a solid dose as a tablet or capsule. Said composition further comprises a pharmaceutically acceptable carrier. Said composition also comprises an angiotensin converting enzyme (i.e., ACE) inhibitor and may alternatively comprise isosorbide mononitrate. Claims additionally each a method to treat a vascular disease characterized by nitric oxide insufficiency via administering a sustained release composition comprising isosorbide nitrate, hydralazine hydochloride and an ACE-inhibitor.

Regarding Claims 1-4, 6-9, 12-13 and 16-25, Cohn's teachings have already been discussed *supra*. Cohn, however, does not teach a composition comprising an isosorbide mononitrate, or a composition comprising ACE-inhibitor and isosorbide dinirate.

Klemsdal et al. teach similar effect of administering either isosorbide dinitrate or isosorbide mononitrate in treating angina pectoris (Figure 1). Furthermore, isosorbide mononitrate "exerts qualitatively similar effects" (See Wikipedia, Pages 1, Lines 36-37).Thus, one skilled in the art will be apprised to substitute isosorbide mononitrate for isosorbide dinitrate, or would even substantiate isosorbide dinitrate with isosorbide mononitrate.

Chobanian et al. teach a composition comprising an ACE inhibitor, a nitric oxide stimulator and at least one pharmaceutically acceptable carrier (Column 3, Lines 55-56) and orally administering said composition to a patient in need thereof (Column 3, Lines 65-66) to treat nitric oxide insufficiency mediated cardiovascular diseases (e.g., arteriosclerotic disorders, secondary hypertension and like; Column 7, Line 60; Column 8, Line 1) . Chobanian et al . further teach that said composition comprises an ACE inhibitors (e.g., captopril, laurel, perindopril) and isosorbide dinitrate (Column 4 Lines 45-49 and 58-59). Chobanian et al. even teach additional anti oxidants(e.g., acerbate, tocopherol and β–carotene; Column 4, Lines 63-64). Choninanian et al. also each that the compositions comprising ACE-

inhibitors, isosorbide dinitrate and a pharmaceutically acceptable carrier may additionally comprise a variety of agents applicable for cardiovascular disease therapy (e.g., anti-anginal agents, calcium channel blocking agens, vasodilators, antihypertensives among others in form of a tablets, coated tablets, capsules or granules (Column 5, Lines 12-41). Thus, Chobanian et al. clearly teach a composition comprising isosorbide dinitrate with an ACE-inhibitor as well as a method to treat a nitric oxide insufficiency mediated cardiovascular disease.

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Cohn according to beneficial teachings from Klemsdal et al., and Chobanian et al. to obtain a sustained release formulation comprising a "low molecule" antioxidant and isosorbide dinitrate, wherein said "low molecular weight antioxidant is hydralazine hydrochloride and a method to treat a cardiovascular disease with the application of said composition; because (i) Klemsdal et al teach that isosorbide mono nitrate and dinitrate produce the same qualitative effect and accordingly one may be substituted for the other and (ii) Chobanian et al. teach a composition comprising isosorbide dinitrate with ACE-inhibitors along with a pharmaceutically acceptable carrier in form of a tablet or capsule and further teach that said composition is orally administered to a patient in need thereof to treat a nitric oxide deficiency mediated cardiovascular disease.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Cohn according to beneficial teachings from Klemsdal et al., and Chobanian et al. to obtain a sustained release composition comprising isosorbide di nitrate and/or mononitrate with hydralazine hydrochloride and an ACE inhibitor with at least one pharmaceutically acceptable carrier to treat a nitric oxide insufficiency-mediated cardiovascular disease; because Klemsdal et al. teach isosorbide dinitrate may be substituted with isosorbide mononitrate and Chobanian et al teach a composition comprising isosorbide dinitrate and an ACE inhibitor in a pharmaceutically acceptable carrier, wherein said composition is in form of a tablet or capsule. Furthermore, the concentration of isosorbide dinitrate and hydralazine hydrochloride disclosed in the prior art references is within the range that is instantly claimed.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

13. For reasons aforementioned, no Claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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19 October 2007

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